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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/925,122	Applicant(s) BANDMAN ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 44-59* is/are pending in the application.

4a) Of the above claim(s) *44,47,49,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 45-46, 48, and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 8 and 44-59 are pending.

2. In view of the amendment filed 11/13/02, the following objections and rejections remain.

3. Claims 44, 47, 49 and 58-59 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. The request for rejoinder of process claims upon allowance of product claims in light of In re Ochiai and In re Brouwer is acknowledged.

5. Claim 8 stands objected to because it depends on non-elected election, which drawn to antibody that binds to SEQ ID NO: 3. The restriction requirement between SEQ ID NO: 1 and SEQ ID NO: 3 is proper for the reasons of record as stated in Paper 6, mailed 6/3/02.

6. Claim 48 stands objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 48 is improper because (1) "**A** composition of claim 46" should have been "**the** composition of claim 46" and (2) wherein the antibody is labeled" in claim 48 fails to further limiting the composition comprising the unlabeled antibody in claim 46.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 50-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of preparing *any* polyclonal antibody with the specificity of the antibody which specifically binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) which binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any polypeptide "having" an amino acid sequence of SEQ ID NO: 1 or any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibodies from said animal and c) screening the isolated antibodies with polypeptide of SEQ ID NO1, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acids sequence of SEQ ID NO: 1, (2) any antibody produced by the method of preparing *any* polyclonal antibody with the specificity of the antibody which specifically binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) which binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with *any* polypeptide "having" an amino acid sequence of SEQ ID NO: 1 or *any* immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibodies from said animal and c) screening the isolated antibodies with polypeptide of SEQ ID NO1, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acids sequence of SEQ ID NO: 1, (3) *any* composition comprising the antibody produced by the method of preparing *any* polyclonal antibody with the specificity of the antibody which specifically binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) which binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any polypeptide "having" an amino acid sequence of SEQ ID NO: 1 or any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibodies from said animal and c) screening the isolated antibodies with polypeptide of SEQ ID NO1, thereby

identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acids sequence of SEQ ID NO: 1 and a suitable carrier, (4) a method of making any monoclonal antibody with the specificity of the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibody producing cells from the animals, c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1, (5) *any* monoclonal antibody produced by the method of making any monoclonal antibody with the specificity of the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibody producing cells from the animals, c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1, (6) *any* composition comprising the monoclonal antibody produced by the method of making any monoclonal antibody with the specificity of the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the

antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibody producing cells from the animals, c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1 and a suitable carrier, (7) the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity" wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library for *any* detection assays or for treating *any* disease. The specification discloses only a method of how to make and use a polyclonal, monoclonal, chimeric, humanized antibody which specifically binds to a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 and 3 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody for diagnostic and detection assays (See page 31-32).

With the exception of the specific antibody that binds to a polypeptide comprising SEQ ID NO: 1 or 3, there is insufficient written description about the structure associated with function of a method of making polyclonal or monoclonal antibody by immunizing an animal with a polypeptide "having" an amino acid sequence of an immunogenic fragment of SEQ ID NO: 1 for in vivo treatment of any disease or for diagnostic assays. The term "having" is open-ended. It expands the immunogenic fragment to include additional amino acids at either end. There is inadequate written description about the additional undisclosed amino acids to be added to the immunogenic fragment. Further, the sequence listing disclosed only full-length polypeptide of SEQ ID NO: 1 and 3. Given the lack of any immunogenic polypeptide fragment and additional representative species of polypeptide other than the polypeptide of SEQ ID NO: 1 and 3 to which the antibody binds wherein the antibody is polyclonal, monoclonal, chimeric, humanized, Fab fragment, F(ab')2 fragment thereof, one of skill in the art would reasonably conclude that the

disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/13/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 8 has been amended.

However, claims 50 and 53 still recite "having". There is insufficient written description about the structure associated with function of a method of making polyclonal or monoclonal antibody by immunizing an animal with a polypeptide "having" an amino acid sequence of an immunogenic fragment of SEQ ID NO: 1 for in vivo treatment of any disease or for diagnostic assays. The term "having" is open-ended. It expands the immunogenic fragment to include additional amino acids at either end. There is inadequate written description about the additional undisclosed amino acids to be added to the immunogenic fragment. Further, the sequence listing disclosed only full-length polypeptide of SEQ ID NO: 1 and 3. Given the lack of any immunogenic polypeptide fragment and additional representative species of polypeptide other than the polypeptide of SEQ ID NO: 1 and 3 to which the antibody binds wherein the antibody is polyclonal, monoclonal, chimeric, humanized, Fab fragment, F(ab')2 fragment thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 8 and 50-52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, page 93).

Chan *et al* teach a biologically active or immunogenic fragment of FBP17 such as residues TCP to PTSYV comprising an amino acid sequence at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular). Further, Chan *et al* teach a biologically active or immunogenic fragment such as APPTPPPLPP (page 1046, Fig 1, 1048, column 1, first paragraph, in particular) and the reference fragments functionally resemble SH3 domain, which is useful for regulating limb and kidney development (See page 1045, in particular).

The claimed invention as recited in claim 8 differs from the reference only by the recitation that an isolated antibody which specifically binds to a biologically active fragment or an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO: 1 or to a biologically active fragment or an immunogenic fragment of a polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO: 1.

The claimed invention as recited in claim 50 differs from the reference only by the recitation that a method of preparing a polyclonal antibody that binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein the antibody binds to an epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein the method comprising: immunizing an animal with a polypeptide having an immunogenic fragment thereof of SEQ ID NO: 1.

The claimed invention as recited in claim 52 differs from the reference only by the recitation that a composition comprising a polyclonal antibody with the specificity mentioned above and a suitable carrier.

Harlow *et al* teach a method of producing polyclonal antibody to any antigen by immunizing an animal with any peptide conjugated to KLH (See page 93, in particular). Harlow *et al* further teach that for practical reasons, rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. Harlow *et al* teach a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce polyclonal antibody as taught by Harlow *et al* with the immunogenic fragment such as residues TCP to PTSYV of FBP17 as taught by Chan *et al* for a composition comprising an antibody and a carrier as taught by Harlow *et al* for an isolated antibody that binds to any epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 and said sequence has HS3C activity. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified (See page 93, in particular). Chan *et al* teach that the reference FBP17 polypeptide fragment is most homologous to the SH3 domain that binds to the consensus proline rich sequences such as APPTPPPLPP (page 1048, column 1, first paragraph, in particular) and functionally resemble SH3 domain which is useful for regulating limb and kidney development (See page 1045, in particular). The term "having" is open-ended. It expands the immunogenic fragment to include additional amino acids at either or both ends to read on the fragment as taught by Chan et al.

Applicants' arguments filed 11/13/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 8 has been amended.

However, Claim 50 recites the method of making any antibody by immunizing any fragment of SEQ ID NO: 1 and the claimed antibody has the binding specificity of claim 8 such as any epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. Further, The term "having" is open-ended. It expands the immunogenic fragment to include additional amino acids at either or both

ends to read on the fragment as taught by Chan et al. Harlow *et al* teach a method of producing polyclonal antibody to any antigen by immunizing an animal with any peptide conjugated to KLH (See page 93, in particular). Harlow *et al* further teach that for practical reasons, rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. Harlow *et al* teach a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays.

In the absence of a side by side comparison, the antibody appears to bind to the claimed sequence because it has a stretch of amino acid sequence that is identical to the reference polypeptide (See residues TCP to PTSYV comprising an amino acid sequence at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular) and the reference polypeptide has HS3C activity since it has proline rich sequence that binds to the SH3 domain containing polypeptides as defined on page 54 at lines 19-21 of the specification.

12. Claims 45, 46 and 48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 319-356, and 626-629).

The teachings of Chan *et al* have been discussed supra.

The claimed invention as recited in claim 45 differs from the reference only by the recitation that the antibody is a Fab fragment, a F(ab')2 fragment.

The claimed invention as recited in claim 46 differs from the reference only by the recitation of a composition comprising said antibody and an acceptable excipient.

The claimed invention as recited in claim 48 differs from the reference only by the recitation the antibody is labeled.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See

page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment such as Fab or F(ab')2 or to label any antibody as taught by Harlow *et al* with the polyclonal antibody that binds specific to any epitope of a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular) and the labeled antibody can be used for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Applicants' arguments filed 11/13/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 8 has been amended.

However, Claim 50 recites the method of making any antibody by immunizing any fragment of SEQ ID NO: 1 and the claimed antibody has the binding specificity of claim 8 such as *any* epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. Further, The term "having" is open-ended. It expands the immunogenic fragment to include additional amino acids at either or both ends to read on the fragment as taught by Chan et al. Harlow *et al* teach a method of producing polyclonal antibody to any antigen by immunizing an animal with any peptide conjugated to KLH (See page 93, in particular). Harlow *et al* further teach that for practical reasons, rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. Harlow *et al* teach a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays.

In the absence of a side by side comparison, the reference antibody appears to bind to the claimed sequence because it has a stretch of amino acid sequence that is identical to the reference polypeptide (See residues TCP to PTSYV comprising an amino acid sequence at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular) and the reference polypeptide has HS3C activity since it has proline rich sequence that binds to the SH3 domain containing polypeptides as defined on page 54 at lines 19-21 of the specification.

13. Claim 45 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The teachings of Chan *et al* have been discussed supra.

The claimed invention in claim 45 differs from the reference only by the recitation that the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody or a polypeptide fragment (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent that binds specifically binds to any epitope of a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Applicants' arguments filed 11/13/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 8 has been amended.

However, the claimed antibody has the binding specificity of any epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. Chan et al teach a polypeptide that has a stretch of amino acid sequence that is identical to the reference polypeptide (See residues TCP to PTSYV comprising an amino acid sequence at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular) and the reference polypeptide has HS3C activity since it has proline rich sequence that binds to the SH3 domain containing polypeptides as defined on page 54 at lines 19-21 of the specification.

14. Claims 45, 56 and 57 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of US Pat No. 6,180,370B, filed June 1995; PTO 892).

The teachings of Chan *et al* have been discussed supra.

The claimed invention in claim 45 differs from the reference only by the recitation that the antibody is a chimeric antibody, a humanized antibody.

The claimed invention in claim 56 differs from the reference only by the recitation that the antibody is produced by screening a Fab expression library.

The claimed invention in claim 57 differs from the reference only by the recitation that the antibody is produced by screening a recombinant immunoglobulin library.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular) by screening a Fab expression library or a recombinant immunoglobulin library. The reference chimeric antibody comprising a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody or humanized antibody as taught by the '370 patent that binds specifically binds to any epitope of a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Applicants' arguments filed 11/13/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 8 has been amended.

However, the claimed antibody has the binding specificity of *any* epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. Chan et al teach a polypeptide that has a stretch of amino acid sequence that is identical to the reference polypeptide (See residues TCP to PTSYV comprising an amino acid sequence at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular) and the reference polypeptide has HS3C activity since it has proline rich sequence that binds to the SH3 domain containing polypeptides as defined on page 54 at lines 19-21 of the specification.

15. Claims 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

The teachings of Chan et al have been discussed supra.

The claimed invention as recited in claim 53 differs from the reference only by the recitation that a method of making monoclonal antibody that binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of

SEQ ID NO: 1 wherein the antibody binds to an epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 wherein the method comprising: immunizing an animal with a polypeptide having an immunogenic fragment thereof of SEQ ID NO: 1.

The claimed invention as recited in claim 54 differs from the reference only by the recitation of a monoclonal antibody produced by the method of claim 53.

The claimed invention as recited in claim 55 differs from the reference only by the recitation a composition comprising the monoclonal antibody and a suitable carrier.

Harlow *et al* teach a method of producing monoclonal antibody (See page 139-149, in particular) and the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Harlow *et al* further teach labeling any antibody with various label such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354 in particular) or NaCl, which is a saline solution (See page 346) for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody that binds to any epitope of a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 and has HS3C activity as taught by Chan *et al* and a composition comprising said antibody and a carrier such as PBS as taught by Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

Applicants' arguments filed 11/13/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 8 has been amended.

However, the claimed antibody has the binding specificity of *any* epitope of a polypeptide having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. Chan et al teach a polypeptide that has a stretch of amino acid sequence that is identical to the reference polypeptide (See residues TCP to PTSYV comprising an amino acid sequence at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular) and the reference polypeptide has HS3C activity since it has proline rich sequence that binds to the SH3 domain containing polypeptides as defined on page 54 at lines 19-21 of the specification.

16. The following new ground of rejection is necessitated by the amendment filed 11/13/02.

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 8, 45-46, 48 and 50-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated antibody which specifically binds to a purified polypeptide comprising an amino acid sequence of SEQ ID NO: 1 and 3 and (2) a method making said antibody for diagnostic assays, **does not** reasonably provide ennoblement for (1) *any* isolated antibody selected from the group consisting of: a) *any* antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", (2) *any* isolated antibody selected from the group consisting of: a) *any* antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the

antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity" wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment or a humanized antibody, (3) *any* composition comprising *any* isolated antibody selected from the group consisting of: a) an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity" and an acceptable excipient, (4) the composition mentioned above wherein the antibody is labeled, (5) a method of preparing *any* polyclonal antibody with the specificity of the antibody which specifically binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) which binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any polypeptide "having" an amino acid sequence of SEQ ID NO: 1 or any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibodies from said animal and c) screening the isolated antibodies with polypeptide of SEQ ID NO1, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acids sequence of SEQ ID NO: 1, (6) any antibody produced by the method of preparing *any* polyclonal antibody with the specificity of the antibody which specifically binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) which binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with *any* polypeptide "having" an amino acid sequence of SEQ ID NO: 1 or *any* immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibodies from said animal and c) screening the isolated antibodies with polypeptide of SEQ ID NO1, thereby identifying a

polyclonal antibody which binds specifically to a polypeptide having an amino acids sequence of SEQ ID NO: 1, (7) *any* composition comprising the antibody produced by the method of preparing *any* polyclonal antibody with the specificity of the antibody which specifically binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) which binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any polypeptide "having" an amino acid sequence of SEQ ID NO: 1 or any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibodies from said animal and c) screening the isolated antibodies with polypeptide of SEQ ID NO1, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acids sequence of SEQ ID NO: 1 and a suitable carrier, (8) a method of making any monoclonal antibody with the specificity of the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibody producing cells from the animals, c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1, (9) *any* monoclonal antibody produced by the method of making any monoclonal antibody with the specificity of the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having

HS3C activity", the method comprising a) immunizing an animal with any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibody producing cells from the animals, c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1, (10) *any* composition comprising the monoclonal antibody produced by the method of making any monoclonal antibody with the specificity of the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity", the method comprising a) immunizing an animal with any immunogenic fragment thereof, under conditions to elicit an antibody response, b) isolating antibody producing cells from the animals, c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody producing hybridoma cells, d) culturing the hybridoma cells and e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence of SEQ ID NO: 1 and a suitable carrier, (11) the antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1, and b) *any* antibody which specifically binds to a polypeptide comprising *any* "naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1, wherein the antibody binds to *any* "epitope" of *any* "polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1, said naturally occurring amino acid having HS3C activity" wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library for *any* detection assays or for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of how to make and use a polyclonal, monoclonal, chimeric, humanized antibody which specifically binds to a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 and 3 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody for diagnostic and detection assays (See page 31-32). The specification discloses HS3C activity as measuring the binding of HS3C to radiolabeled formin polypeptides containing the proline-rich region (See page 54 at lines 19-21, in particular).

The specification does not teach how to make *any* antibody that binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1 and *any* "epitope" of a polypeptide "having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 because there is sufficient guidance as the antigenic determinant (i.e. the specific amino acid sequence of the immunogen or polypeptide fragment) used by applicant to make any antibody mentioned above that binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1 or *any* "epitope" of a polypeptide having 10% difference (90% identity) in the amino acid sequence of SEQ ID NO:1, which is equivalent to having 26-27 amino acid difference in SEQ ID NO: 1. Further, the term comprising or having is open-ended. It expands the "immunogenic fragment" to include additional amino acids at either or both ends. There is insufficient guidance as to the undisclosed amino acid added to the immunogenic fragment for making antibody that binds to the full-length polypeptide of SEQ ID NO: 1 or any polypeptide having 10% difference in the amino acid sequence of SEQ ID NO:1, which is equivalent to having 26-27 amino acid difference in SEQ ID NO: 1, or any epitope of said polypeptides. There are no working examples in the specification as filed that the claimed antibody ever been made, much less demonstrating the binding specificity of the claimed antibody, in turn, would be useful for detection assays.

Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization

with a peptide fragment may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Without the specific amino acid residues of the immunogen used by applicant, it is unpredictable to determine which antibody generated from any immunogenic fragment having additional undisclosed amino acid would binds specifically to a polypeptide of SEQ ID NO: 1, a polypeptide comprising a naturally-occurring amino acid sequence such as having 90% sequence identity to SEQ ID NO: 1 wherein the naturally occurring amino acid sequence binds having "HS3C activity" or *any* epitope of a polypeptide of SEQ ID NO: 1 or any epitope of a polypeptide comprising a naturally-occurring amino acid sequence such as having 90% sequence identity to SEQ ID NO: 1 wherein the naturally occurring amino acid sequence binds having "HS3C activity".

With regard to "having HS3C activity", the specification discloses HS3C activity as measuring the binding of HS3C to the proline-rich region of a radiolabeled formin polypeptides that interacts with the SH3 containing protein (See page 54 at lines 19-21, in particular). However, binding does not equal to functions since any polypeptide can bind to any proline-rich region of the formin polypeptide, much less a polypeptide having 90% sequence identity to SEQ ID NO: 1 or 26-27 amino acid difference to SEQ ID NO: 1.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

It is known in the art that even a single amino acid difference in a polypeptide would produce antibody that fails to bind to said polypeptide. Since the amino acid sequence of the immunogen used by applicant is not disclosed and the specificity of said antibody is not enabled, it follows that the method of making and using the antibody with unknown specificity is not enabled.

With regard to composition comprising *any* polyclonal or monoclonal antibody with the specificity mentioned above and an acceptable excipient or suitable carrier, the specification fails

to provide any *in vivo* working examples, or guidance with respect to treating a patient suffering from *any* specific disease using *any* antibody mentioned above. Given the indefinite number of undisclosed disease or conditions that may or may associated with the expression of "HS3C" and the lack of guidance as to the function of SEQ ID NO: 1 or a polypeptide having a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO: 1 having binding activity to the proline-rich region of a radiolabeled forming polypeptide that binds to SH3 domain containing proteins, further research is required. Since the composition comprising said antibody is not enabled, it follows that composition comprising the labeled antibody is not enabled.

The '370 patent teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular). In the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as serum sickness which prohibitive to the use of antibody for such treatment. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/13/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the specification provides extensive teaching on how to make and use antibodies see for example, page 9, lines 1-9, page 31, lines 20-25 and page 38, lines 27 to page 39, line 4. (2) the specification describes how to make variants to the amino acid sequences of SEQ ID NO: 1, including variants having 90% sequence identity to SEQ ID NO: 1, as well as fragment of SEQ ID NO: 1 having biological or immunogenic activity. (3) the

specification teaches antibodies to variants or fragments of the amino acid sequence of SEQ ID NO: 1 can used for drug screening purpose (See page 46 lines 3-15), page 46 lines 14-15 states that "antibodies can be sued to detect the presence of any peptide which shares one or more antigenic determinants with HS3C" (4) Applicants have rewritten claim 8 in independent form and have included the functional language of "having HS3C activity".

However, the amendment to claim 8 fails to overcome the enablement rejection because of the following reasons:

(1) the amended claim 8 recites the antibody that binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1 or any "epitope" of a polypeptide "having a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1 since there is sufficient guidance as the antigenic determinant (i.e. the specific amino acid sequence of the immunogen or polypeptide fragment) used by applicant to make any antibody mentioned above that binds to *any* "epitope" of a polypeptide of SEQ ID NO: 1 or *any* "epitope" of a polypeptide having 10% difference (90% identity) in the amino acid sequence of SEQ ID NO:1, which is equivalent to having 26-27 amino acid difference in SEQ ID NO: 1.

(2) With regard to functional language of "having HS3C activity", the specification discloses HS3C activity as measuring the binding of HS3C to the proline-rich region of a radiolabeled formin polypeptides that interacts with the SH3 containing protein (See page 54 at lines 19-21, in particular). However, binding does not equal to functions since any polypeptide can bind to any proline-rich region of the formin polypeptide, much less a polypeptide having 90% sequence identity to SEQ ID NO: 1 or 26-27 amino acid difference to SEQ ID NO: 1. Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Skolnick *et al* teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Since the amino acid sequence of the immunogen used by applicant is not disclosed and the specificity of said antibody is not enabled, it follows that the method of making and using the antibody with unknown specificity is not enabled.

(3) The term "comprising" or "having" is open-ended. It expands the "immunogenic fragment" in claims 50 and 53 to include additional amino acids at either or both ends. There is insufficient guidance as to the undisclosed amino acid added to the immunogenic fragment for making antibody with the specificity of binding to the full-length polypeptide of SEQ ID NO: 1 or antibody that binds to any polypeptide having 10% difference in the amino acid sequence of SEQ ID NO:1, which is equivalent to having 26-27 amino acid difference in SEQ ID NO: 1, or *any* epitope of the full-length polypeptide of SEQ ID NO: 1 or any epitope of a polypeptide having 10% difference in the amino acid sequence of SEQ ID NO:1, which is equivalent to having 26-27 amino acid difference in SEQ ID NO: 1.

(4) There are no working examples in the specification as filed that the claimed antibody ever been made, much less demonstrating the binding specificity of the claimed antibody such as the ones recited in claim 8, in turn, would be useful for detection assays.

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any

inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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January 27, 2003

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